Potential Mechanism of Action of Human Growth Hormone on Isolated Human Penile Erectile Tissue

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OBJECTIVES To evaluate the mechanisms of growth hormone (GH) action on isolated human penile erectile tissue. Human GH (hGH) has been suggested to play a role in male reproductive function, including penile erection. Nevertheless, it still remains unclear which intracellular pathways mediate the physiological effects of GH on the human corpus cavernosum (HCC).

METHODS Using the organ bath technique, the effects of GH were investigated on electrical field stimulation (EFS)-induced relaxation of isolated HCC in the absence and presence of the guanylyl cyclase inhibitor 1H-[1,2,4]oxadiazolo[4,3-a]quinoxalin-1-one (ODQ) and nitric oxide synthase (NOS) inhibitor N^G-nitro-L-arginine (L-NOARG, 10 μm). Effects of GH on the production of tissue cyclic guanosine monophosphate (cGMP) in the absence and presence of ODQ and L-NOARG were also elucidated using radioimmunoassay.

RESULTS ODQ and L-NOARG abolished the relaxation of the tissue induced by EFS, whereas amplitudes were increased by physiological concentrations of GH (1-100 nM). The attenuation of EFS-induced amplitudes by L-NOARG but not ODQ was, in part, reversed by GH. The production of cGMP (pmol cGMP/mg protein) induced by 10 nM GH was abolished in the presence of 10 μM ODQ. In contrast, the combination of GH (10 nM) and L-NOARG (10 μM) maintained cGMP production significantly greater than baseline (0.68 ± 0.36 vs 1.07 ± 0.48 pmol cGMP/mg protein).

CONCLUSIONS Our data provide evidence that GH may act on human HCC by an NO-independent effect on guanylyl cyclase activity and may thus explain how growth factors, such as hGH, regulate male erectile function. UROLOGY 75: 968–973, 2010. © 2010 Elsevier Inc.

Human growth hormone (hGH/GH), synthesized in the anterior pituitary gland, is a polypeptide composed of 191 amino acids, with a molecular weight of 21.5 kDa. It has been demonstrated that GH can induce an increase in metabolic activity in different tissues.[1,2] Although not considered a classical sex hormone, GH has been suggested to be involved in sexual maturation and to play a regulatory role in male reproductive function. GH not only mediates the secretion of the luteinizing hormone and follicle-stimulating hormone but also has a physiological significance in early testosterone stimulation.[3,4] Because GH is also produced extrapituitary in gonadal and mammary tissues, this indicates a local autocrine or paracrine action of the hormone in the reproductive tract. GH deficiency may lead to fatigue, loss of sexual desire and erections, and oligospermia or azoospermia.[5,6] It is assumed that the biological effects of GH include the stimulation of endothelial nitric oxide (NO) formation. In fact, there is some evidence in favor of this hypothesis: Böger et al[7] (1996) reported that treatment of GH-deficient patients with recombinant GH (rGH) resulted in an increase in systemic NO metabolites, enhanced urinary excretion of cyclic guanosine monophosphate (cGMP), and had beneficial effects on the cardiovascular system. Because several studies have shown that alterations in the expression of growth factors are associated with development and aging, it has been suggested that they may also play a role in the etiology of erectile dysfunction.[8,9] With regard to human penile erectile tissue, Becker et al[10] (2000) demonstrated that physiological doses of recombinant GH elicited dose-dependent relaxation of isolated human corpus cavernosum (HCC) strips. This relaxing potency was paralleled by severalfold increase in tissue levels of

Results were presented on the occasion of the Winter Scientific Meeting of the Sexual Medicine Society of North America (SMSNA), Chicago, IL, United States, 06.12-09.12.2007, and awarded with the ABSTRACT AWARD.

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Submitted: December 18, 2008, accepted (with revisions): May 20, 2009

0090-4295/10/$34.00
doi:10.1016/j.urology.2009.05.046

cGMP. Moreover, they were able to show that the levels of GH in the systemic and cavernous blood (plasma) of healthy male subjects increased during sexual arousal, when the flaccid penis became tumescent. In contrast, this increase in the systemic circulation and cavernous compartment was found to be negligible in patients with an organogenic erectile dysfunction. They considered their findings to be a strong evidence that GH might be of significance in the maintenance of male erectile capability, probably via the stimulation of cGMP production in human vascular and nonvascular cavernous smooth muscle.[11] Nevertheless, it still remains unclear which intracellular pathways mediate the physiological effects of GH on the HCC. Therefore, the purpose of our study was to evaluate further the mechanisms of GH action on isolated human penile erectile tissue.

MATERIAL AND METHODS

Tissue Source

In accordance with the regulations of the local ethics committee of the Hannover Medical School, human penile erectile tissue (corpus cavernosum) was obtained from 6 patients (mean age 32 years) who had undergone male-to-female gender reassignment surgery. Prior to the surgery, the patients had received for 8-15 months antihormonal (antiandrogenic) and estrogen replacement therapy. The tissue was immediately placed in a chilled organ-protective solution (Custadiol, Dr. Franz Köhler Chemie, GmbH, Alsbach, Germany) and transported to the laboratory for further preparation. All experiments were performed within 12 hours after tissue excision.

Organ Bath Studies

Square tissue strips were applied to an organ bath (IOA 5306, Föhr Medical Instruments, Seeheim, Germany) under standard conditions and challenged by the addition of 1 μM norepinephrine (NE). Strip preparations that did not present a force generation of >5 mN (= 500 mg) were excluded from the protocol. After a stable tension had been reached, the effects of rGH (GENOTROPIN, Pfizer-Pharmacia AB, Stockholm, Sweden) on the relaxation of the isolated HCC, induced by transmural electrical field stimulation (EFS), were investigated both in the absence and presence of the guanylyl cyclase (sGC) inhibitor 1H-[1,2,4]oxadiazolo[4,3-a]quinoxalin-1-one (ODQ, 10 μM) and nitric oxide synthase (NOS) inhibitor N^G-nitro-L-arginine (L-NOARG, 10 μM). EFS parameters were set as follows: Frequency 10 Hz, supramaximal current, 0.8 millisecond pulse, 5-second train, train interval 120 seconds. Concentration-response curves were examined on n = 6-8 cavernous strip preparations originating from at least 2 different patients. In this protocol, the nitric oxide donor drug sodium nitroprusside (SNP) and sildenafil nitrate (NCX 911), a nitrosylated derivative of the phosphodiesterase type 5 (PDE5, cG-PDE) inhibitor sildenafil, were used as reference compounds.[12]

Assays for Cyclic GMP

To determine dose-dependent effects of GH on the production of tissue cyclic GMP both in the absence and presence of ODQ or L-NOARG, HCC strip preparations were allowed to equilibrate for 60 minutes in Krebs buffer maintained at a temperature of 37°C and continuously gassed with 95% O_2 and 5% CO_2. The strips were then transferred into 2-mL reaction vials containing Krebs buffer and maintained under the same conditions. Twenty minutes after the addition of NE (1 μM), the tissue was exposed to rGH (0.01 μM), sodium nitroprusside (0.01 and 1 μM), rGH + 10 μM ODQ or L-NOARG, or SNP + 10 μM ODQ. At the end of the incubation period, the tissue was rapidly frozen in liquid nitrogen, homogenized in the frozen state and cGMP was extracted using 80% ethanol. After centrifugation at 3000g, the ethanolic phase was removed and lyophilyzed. The remaining dry particulate fraction was resuspended in 50 mM sodium acetate buffer and assayed for cyclic GMP using a specific radioimmunoassay (IBL, GmbH, Hamburg, Germany). Each drug concentration was tested 3- to 6-fold and each sample was assayed in duplicate. The protein content of the particulate fractions was determined using the Pierce BCA Protein Assay (Pierce, Rockford).

Chemicals

SNP and L-NOARG were obtained from Sigma Chemical Co. (St. Louis), TTX and ODQ from Tocris Cookson Bioscience, Ltd. (Bristol, UK), and norepinephrine-HCl (NE, Arterenol) was supplied by Sanofi-Aventis Deutschland GmbH (Frankfurt, Germany). Sildenafil nitrate (NCX 911) was generously provided by NicOx Pharmaceuticals SA (Sophia Antipolis, France). All other laboratory chemicals were obtained from Merck KGaA (Darmstadt, Germany) or CLARIANT AG (Muttenz, Switzerland). Stock solutions of the drugs were prepared using Krebs buffer (rGH, SNP) or DMSO (L-NOARG, ODQ, sildenafil) and further diluted using either saline (0.9% NaCl, DeltaSelect, GmbH, Dreieich, Germany) or Krebs buffer.

Analysis of Data

Responses of the SV tissue subjected to EFS and the drugs (L-NOARG, ODQ, rGH, SNP, sildenafil citrate) are expressed as percent change in amplitude height. All data are given as mean ± standard deviation of the mean (SD). The Gosset *t* test was used to compare mean values from data cohorts from the organ bath studies. $P \leq .05$ was considered statistically significant.

RESULTS

Organ Bath Studies

Approximately 30% of the cavernous tissue strips showed spontaneous phasic contractile activity, which attenuated during the equilibration period (60-90 minute). The sodium channel blocker tetrodotoxin (TTX), guanylyl cyclase inhibitor ODQ, and NOS inhibitor L-NOARG abolished the phasic relaxation of the tissue induced by EFS (Fig. 1), thereby confirming that the tissue response to electrical stimulation was of neurogenic origin and mediated via nitrinergic pathways (NO synthase, NO, and cyclic GMP). The amplitudes of relaxation were significantly increased by the addition of physiological concentrations of the nitrovasodilator SNP (1-100 nM) and recombinant human growth hormone (rGH, 10 nM-10 μM). At concentrations of 1 and 10 μM, the effects of rGH on isolated corpus cavernosum were similar to

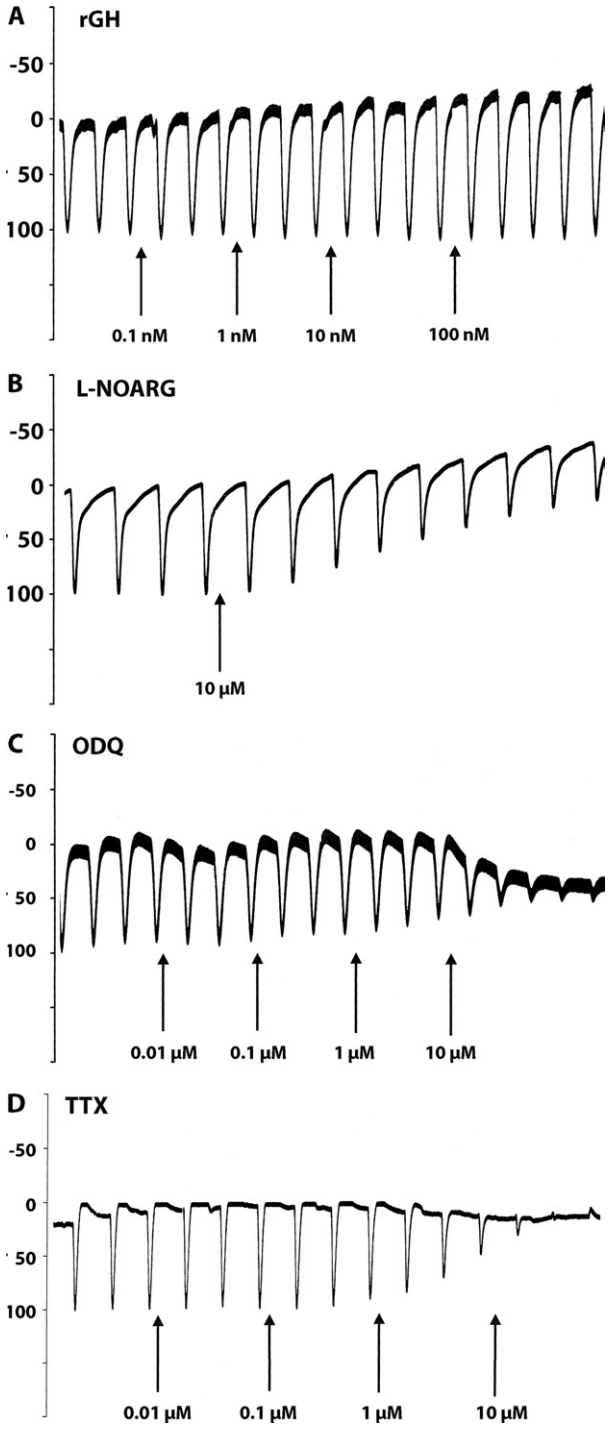

Figure 1. Original traces of organ bath experiments presenting the effects of increasing concentrations of recombinant human growth hormone (rGH, 0.1-100 nm) **(A)**, nitric oxide synthase inhibitor L-NOARG (10 μm) **(B)**, guanylyl cyclase inhibitor ODQ (0.01-10 μm) **(C)**, and Na^+ channel blocker tetrodotoxin (TTX, 0.01-10 μm) **(D)** on the phasic relaxation induced by transmural electrical field stimulation (EFS) of norepinephrine-contracted isolated HCC tissue strips. 100 = magnitude of the EFS-induced amplitude in the absence of drugs; y axis: positive scale bar indicates EFS-induced relaxation and negative scale bar indicates contractile response.

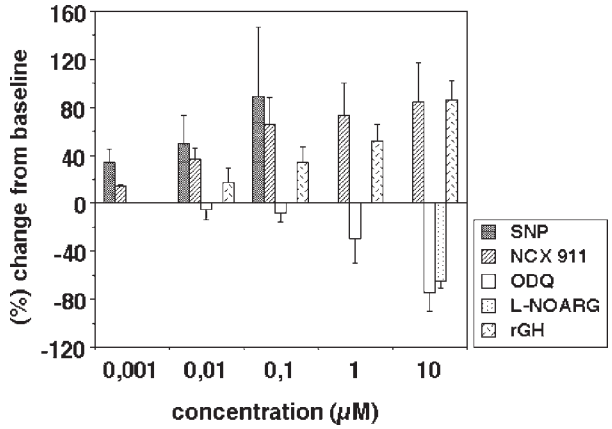

Figure 2. Effects of increasing concentrations of the nitrovasodilator SNP, PDE5 inhibitor sildenafil nitrate (NCX 911), sGC inhibitor ODQ, nitric oxide synthase inhibitor L-NOARG, and recombinant human growth hormone (rGH) on EFS-induced relaxation of isolated HCC strips. Baseline = height of amplitudes in the absence of drugs. Positive bar scale indicates increase in EFS-induced amplitudes. Negative bar scale indicates attenuation of EFS-induced amplitudes. n = 6-8 tissue strips were tested for each drug.

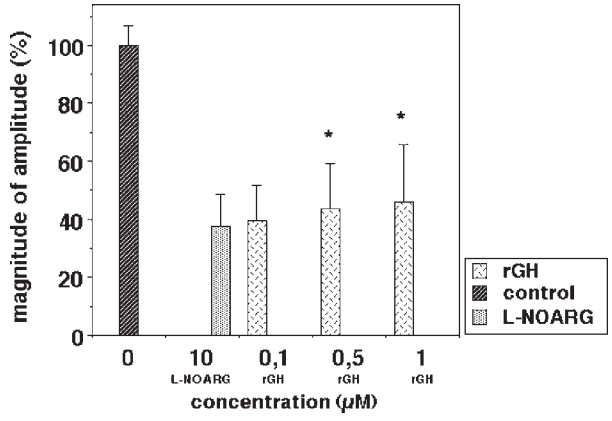

Figure 3. Effects of rGH (0.1, 0.5, and 1 μm) on the inhibition induced by L-NOARG (10 μm) of the phasic relaxation exerted by EFS of isolated HCC strips. 0 = control, magnitude of the amplitude induced by EFS in the absence of drugs. n = 4 tissue strips were used to generate the dose-response curve. *Indicates that the response of the tissue to rGH in the respective concentration is significantly different from the response registered after the addition of L-NOARG.

those exerted by the PDE5 inhibitor sildenafil nitrate: 1 and 10 μM of rGH increased mean peak amplitude of phasic relaxation by 51.6% ± 13.4% and 85.4% ± 16.7% over baseline, respectively. In the presence of 1 and 10 μM sildenafil, the increase amounted to 72.6% ± 27.3% and 84% ± 33.1%, respectively (Fig. 2). Interestingly, the attenuation of the relaxation amplitudes induced by EFS by L-NOARG (10 μM) was, in part, reversed by rGH at concentrations of 0.5 and 1 μM (Fig. 3). In contrast, rGH had no effect on the inhibition brought about by ODQ of the phasic relaxations (data not shown).

Assays for cGMP

Exposure of the CC strip preparations to 0.01 μM (10 nM) of rGH resulted in a 6-fold increase in cyclic GMP (control = 0.68 ± 0.36 pmol cGMP/mg protein). In contrast, the increase in cGMP levels induced by SNP was significantly lower. Exposure to 0.01 and 1 μM SNP for 10 minutes resulted in 2- and 4-fold increase, respectively, in the production of cyclic GMP. Not surprisingly, the generation of cyclic GMP induced by SNP was almost completely abolished in the presence of the guanylyl cyclase inhibitor ODQ (10 μM). The accumulation of cyclic GMP induced by 10 nM GH (3.76 ± 2.0 pmol cGMP/mg protein) was also significantly attenuated in the presence of 10 μM ODQ (mean: 0.32 ± 0.19 pmol cGMP/mg protein). In contrast, the combination of GH (10 nM) + L-NOARG (10 μM) maintained cyclic GMP production significantly above baseline (0.68 ± 0.36 vs 1.07 ± 0.48 pmol cGMP/mg protein) (Fig. 4A and B).

COMMENT

Hormones, such as human growth hormone and insulin-like growth factors (IGF), are involved in the maintenance of various tissue functions and may also play a role in different pathological conditions. There is also evidence that GH might directly or indirectly affect the function of vascular smooth muscle via an enhancement of the NO—cyclic GMP system. Böger et al[7] (1996) demonstrated that treatment of GH-deficient patients, characterized by high serum cholesterol and/or triglyceride concentrations, low HDL cholesterol levels, and a 2-fold higher risk of death from cardiovascular disease, with rGH increased systemic NO and urinary cGMP excretion and had beneficial effects on overall cardiovascular function. Böger et al[7] supposed that NO production is impaired in adult patients with untreated GH deficiency and speculated that the beneficial effects of GH in these patients might be mediated via the stimulation of endothelial NO formation, which concomitantly decreased peripheral arterial resistance.[13] A significance of GH in the control of the male and female reproductive function, especially the maintenance of penile erection, has also been suggested. Hamed et al[14] (2003) measured the levels of GH, NO, and cyclic GMP in the cavernous blood obtained from the flaccid penis of diabetic and nondiabetic patients with ED and in the systemic venous blood of patients and healthy subjects. They found that in diabetic and nondiabetic patients with ED, the levels of GH, NO, and cyclic GMP were lower compared with the levels in healthy male subjects. Systemic NO was positively correlated with GH and cyclic GMP. In vitro experimental studies showed a significant dose-dependent relaxation of isolated human cavernous smooth muscle challenged by the alpha-adrenoceptor agonist norepinpehrine in response to the cumulative addition of rGH. This relaxing potency of the hormone was paralleled by its ability to elevate intracellular levels of cyclic GMP. The observation that serum levels of GH increased

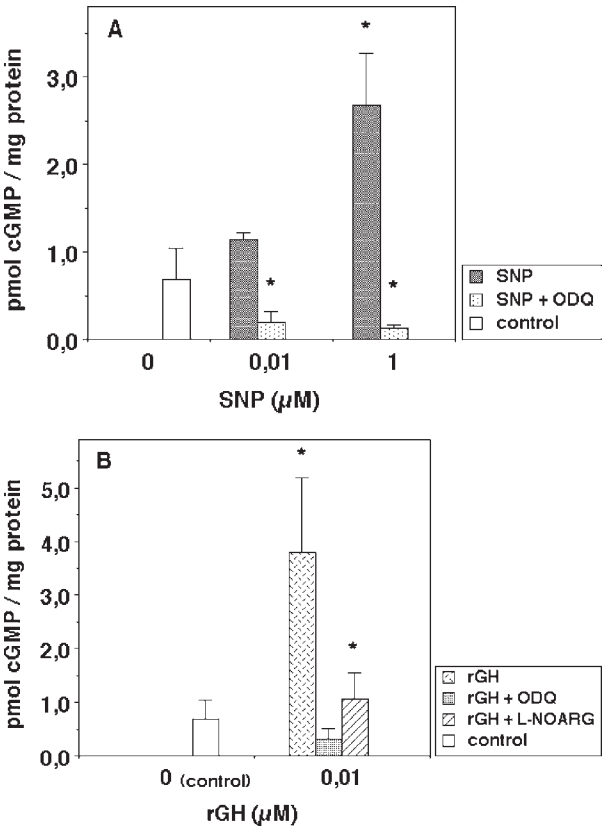

Figure 4. Accumulation of cyclic GMP in isolated HCC tissue strips by SNP (0.01, 1 μM) **(A)** and recombinant human growth hormone (rGH, 10 nM) **(B)** in the absence and presence of the guanylyl cyclase inhibitor ODQ and NOS inhibitor L-NOARG (10 μM). **(B)** 0 = control, represents basal NO-dependent cGMP production; scattered bar represents stimulation of basal cGMP production by 10 nM of rGH, dotted bar represents inhibition of basal NO-dependent cGMP production by ODQ, striped bar represents inhibition of NO-dependent cGMP production by L-NOARG which is, in part, compensated by the rGH-mediated activation of sGC. *Indicates that cGMP level is significantly different from control.

in the cavernous and systemic blood of 35 healthy male volunteers during sexual arousal, in the phase of penile tumescence, also gives rise to a possible involvement of the hormone in the induction of penile erection.[10] Interestingly, the increase in GH registered in the healthy males with the beginning of sexual arousal was found to be negligible in subjects with an organogenic cause of ED.[11] These findings added further support to the hypothesis that disturbances in the secretion of GH may lead to impairment in male erectile capability. Despite these intriguing data from experimental and clinical studies, till date, no study has attempted to further evaluate the potential mechanism of action of GH on human penile erectile tissue. This prompted us to investigate in an in vitro setting, the effects of GH on the electrically induced phasic relaxation and the production of cyclic GMP of isolated HCC in the absence and presence of the guanylyl cyclase inhibitor ODQ and NO synthase inhib-

itor L-NOARG. Our findings are in accordance with the results presented by Becker et al[10] (2000) that GH can enhance the cyclic GMP signaling in HCC. The fact that this protocol and the present study used corpus cavernosum obtained from transsexual patients, who had received hormonal therapy before surgery, raises the question whether such erectile tissue is appropriate to clarify the physiological effects of GH. It has been demonstrated in the rodent model that androgen-deprivation results in penile tissue atrophy (reduction in trabecular smooth muscle content due to replacement of muscle fibers by collagenous fibers), alterations in local nerve structure, and endothelial morphology. Further, androgen deficiency may also give way to the accumulation of adipocytes in the subtunical region of the corpus cavernosum and diminish protein expression and activity of the endothelial and neuronal nitric oxide synthases (eNOS, nNOS).[15,16] However, Becker et al,[10] in their study, not only examined the effects of GH on human penile erectile tissue obtained from patients who had received hormonal therapy but also used cavernous smooth muscle from patients who had undergone surgical correction of penile deviation (Nesbit surgery). They observed no significant differences in the functional responses of the tissue to GH. Our study, for the first time, provides evidence that GH may act via the stimulation of guanylyl cyclase activity that is independent of NO. Indeed, there are few data in support of the hypothesis that the mechanism of action of GH is dependent on the enzyme soluble guanylyl cyclase (sGC). It has been shown earlier that hGH at a concentration of 10 nM enhanced 2- to 4-fold the activity of sGC isolated from skeletal muscle, liver, lung, heart, pancreas, and the kidney cortex of rats.[17] Later, Yoshioka et al[18] (2006) investigated, using microarray analysis, the expression of genes that are supposed to be regulated by GH in the heart of spontaneous dwarf rats. They found that mRNA specifically encoding for the sGC was upregulated in response to treatment of the animals with GH. These results suggest that GH is involved in the control of proteins known to antagonize smooth muscle contractile function and can promote an enhancement of the activity of the sGC/cyclic GMP system. In contrast, contractile effects of GH on erectile tissue have also been reported. Ra et al[19] (1996), using an in vitro setting, registered a dose-related elevation of the tension of isolated canine corpus cavernosum by direct perfusion with GH of porcine origin. The tension induced by GH (1 nM-1 μM) amounted to 110% of the contraction produced by 120 mEq of KCl. However, these findings have to be assessed with caution. Because the study used canine corpora cavernosa, it remains unclear whether GH indeed participates in the induction of penile detumescence in man. Moreover, the authors stated that in the corpus cavernosum of dogs, a cross-binding of GH to prolactin (PRL) receptors cannot be ruled out. This might be due to the expression pattern of PRL- and GH-receptors in the dog penis and the functional homology demonstrated between these receptors.[20] Future studies may reveal whether GH or GH secretagogues can consistently increase the endogenous production of cyclic GMP in human penile erectile tissue in vivo and are efficacious and safe in male subjects with an organogenic cause of ED.[21,22]

CONCLUSIONS

Our study demonstrates that the potency of recombinant hGH (rGH) to stimulate the in vitro functional responses of isolated human trabecular smooth muscle was more sensitive toward the sGC-inhibitor ODQ than to the NOS-inhibitor L-NOARG. This finding provides evidence that hGH may act on HCC by an effect independent of NO on guanylyl cyclase activity. This mechanism may explain how hGH (and putatively other growth factors) is involved in the regulation of male erectile function.

Acknowledgments. To Pfizer-Pharmacia AB (Stockholm, Sweden) for kindly providing recombinant human growth hormone (GENOTROPIN), NicOx S.A. (Sophia Antipolis, France) for providing sildenafil nitrate (NCX 911), and Nicola Jane van Dornick (Hannover, Germany) for editing the linguistic style of the manuscript.

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